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# SYNTHETIC ORGANIC CHEMICALS

PUBLISHED BY THE

Eastman Kodak Company, Rochester, N. Y.

VOLUME 13 • 1941 • NUMBER 1

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## Synthesis of Oligosaccharides

DELBERT D. REYNOLDS

Research Laboratories — Eastman Kodak Company

THE GROUP of compounds that may be visualized as formed by the combination of monosaccharide units, with the loss of water, is classified as oligosaccharides and polysaccharides. An oligosaccharide may be considered as a compound formed from n molecules of a monosaccharide by the loss of n − 1 molecules of water, where n has values of two to five inclusive. The higher members of the series are known as polysaccharides. Examples of combination are—

$$n\,C_6H_{12}O_6 - (n-1)H_2O \rightarrow C_{6n}H_{10n+2}O_{5n+1}$$

$$2\,C_6H_{12}O_6 - H_2O \rightarrow C_{12}H_{22}O_{11}$$ Disaccharide (n = 2)

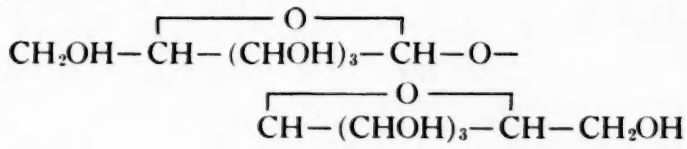
$$3\,C_6H_{12}O_6 - 2\,H_2O \rightarrow C_{18}H_{32}O_{16}$$ Trisaccharide (n = 3)

Attempts to prepare oligosaccharides from monosaccharides date from 1872, when it was found that an unfermentable, amorphous product resulted from the action of acids on a concentrated solution of *d*-glucose. By this method, Fischer, in 1890, prepared a gumlike substance that formed an osazone, and which he named "isomaltose." (Since that time, several compounds have been described under this name; gentiobiose has been isolated from some of them and others have been shown to be impure maltose.) The first actual disaccharide synthesis was effected in 1898, through the use of enzymes.

At the present time, the following methods are recognized as being the most useful for the preparation of oligosaccharides. In most cases, the sugar is obtained as its acetate, which can be hydrolyzed to the free sugar.

### *Condensation Accompanied by Loss of Water*

A monosaccharide is used which has the hydroxyl groups acetylated, except the one where linkage is to be made. It is shaken with phosphorus pentoxide in an inert solvent. This type of synthesis has been used for the preparation of the "trehalose-type" sugars, which are those having the acetal-hydroxyls joined as follows—

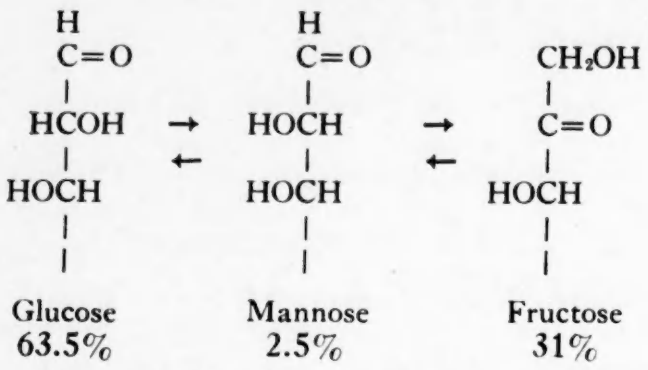


Thus, β-β-trehalose octaacetate has been obtained in 2% yield from β-*d*-glucose-2,3,4,6-tetraacetate. A galactobiose octaacetate of the trehalose type was obtained in 18% yield from β-*d*-galactose-2,3,4,6-tetraacetate. The free sugars were obtained by hydrolysis.

### *Lobry de Bruyn–Van Ekenstein Rearrangement*

Lobry de Bruyn and Van Ekenstein showed that aldose sugars rearrange in weakly alkaline solution, to form ketoses, as well as epimeric aldoses. This rearrangement may be represented by

the following equation in which open-chain formulae are employed—




The reaction has proved exceedingly useful for the preparation of new ketoses in the disaccharide series. By applying this method, Montgomery and Hudson obtained a new disaccharide ketose, lactulose, by the action of saturated aqueous calcium hydroxide on lactose. The change is represented in Figure 1. In a similar way, Austin prepared *d*-glucoheptulose from *d*-glucoheptose.

### *Thermal Condensations*

Pictet and his co-workers synthesized disaccharides by heating simple sugar units in vacuo; in this manner, they obtained maltose from *β-d*-glucose and *α-d*-glucose. Later they employed another method in which equimolecular amounts of glucosan and *β-d*-glucose were heated in vacuo, at 150° C., with or without the addition of zinc chloride. By the latter procedure, 5.0–9.5% yields of maltose were obtained in the form of maltose octaacetate. They also prepared lactose from *β-d*-glucose and either *β-d*-galactose or *β-d*-galactosan. Pictet suggested that the mechanism involves the intermediate formation of an anhydro-monosaccharide that reacts with a molecule of monosaccharide to produce the disaccharide.

### *Enzymatic Condensation*

Hill was the first to use this method of synthesis. By the action of yeast enzyme (*α*-glucosidase) on a 40% *d*-glucose solution, he was able to isolate maltose and "revertose," an isomaltose. Ferments, under suitable conditions, can build up from their constituents the same saccharides that they hydrolyze. Thus, emulsin, in concentrated solutions of glucose, builds up gentiobiose and, in a smaller quantity, cellobiose. Lactobioses have also been made in this way.

### *Bergmann–Schotte Reaction*

Bergmann and Schotte introduced a method of epimerizing sugar molecules —that is, reversing the position of the hydroxyl group on $C_2$—by the action of perbenzoic acid on a glycal. Through the employment of this procedure, a number of new disaccharides, as well as some of the rarer monosaccharides, have been prepared. The necessary glycal may be obtained by the action of zinc dust and glacial acetic acid on the corresponding acetobrom compound, followed by deacetylation.

By application of the Bergmann-

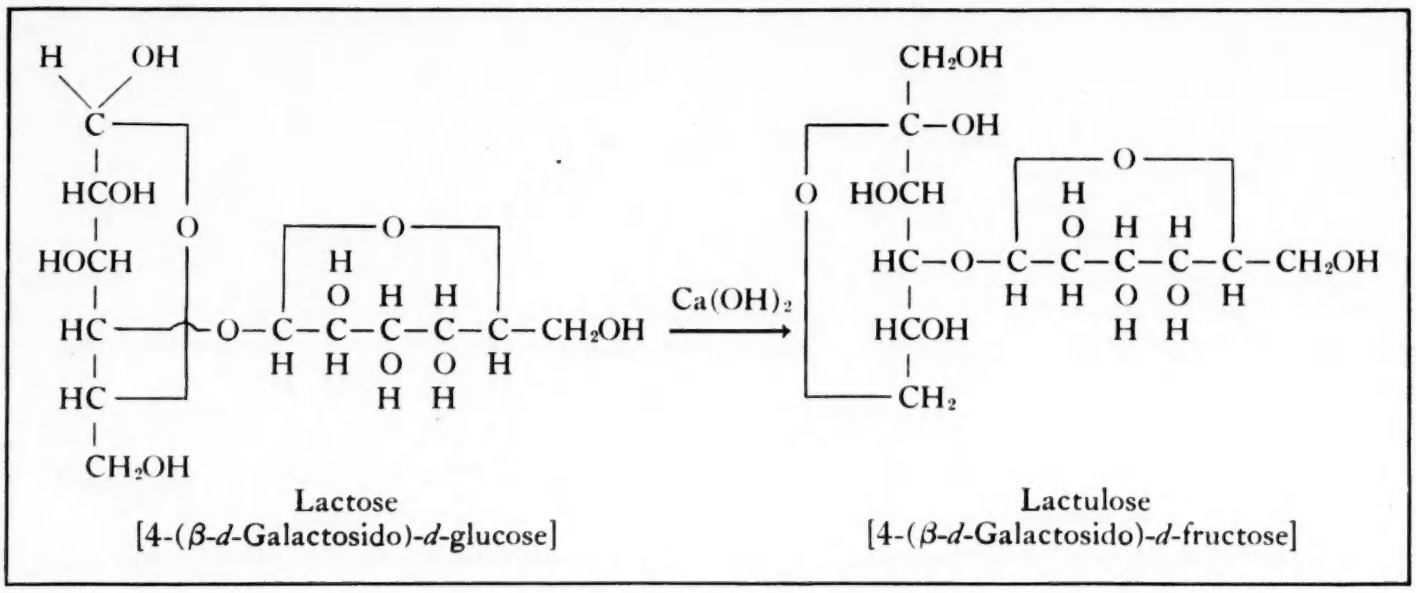
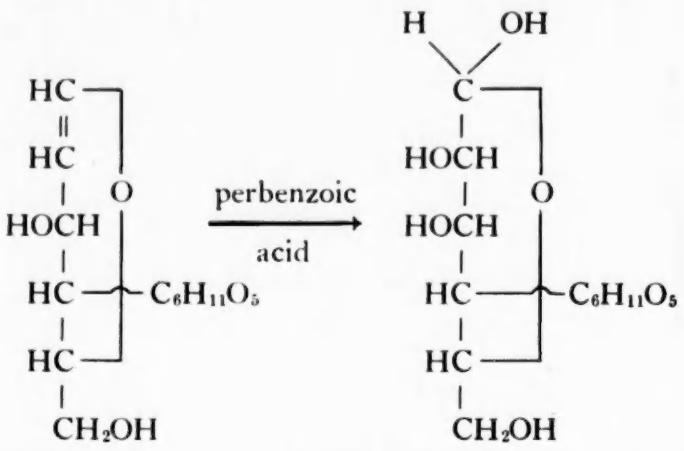



FIGURE 1 — *Reaction involved in the preparation of lactulose from lactose.*

Schotte method, 4-(β-*d*-glucosido)-*d*-mannose was prepared from cellobial, as represented in the following equation—



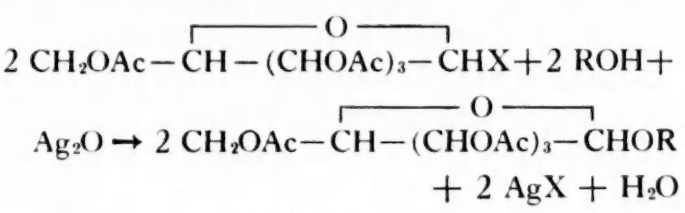

Cellobial — 4-(β-*d*-Glucosido)-*d*-mannose

This reaction does not take place entirely as indicated—that is, with the hydroxyl groups in *cis* positions on $C_2$ and $C_3$; a small amount of cellobiose is also formed. When the glycal is unsubstituted, the *cis* configuration predominates; in this case the *cis* product is obtained in 90% yield. On the other hand, if acetyl or methoxyl groups are substituted for the hydroxyls, the *trans* configuration predominates.

This reaction has also been used for the preparation of 4-(β-*d*-galactosido)-*d*-mannose from lactose, and 6-(β-*d*-glucosido)-*d*-mannose from gentiobiose.

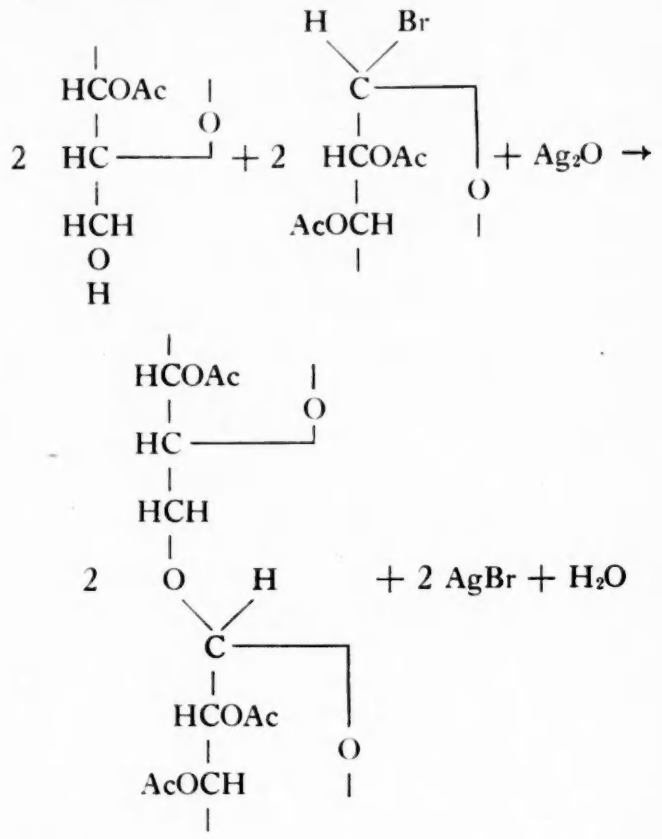
### *Königs–Knorr Reaction*

The Königs-Knorr reaction was originally used for the preparation of glycosides. Essentially, the method is one in which an acetohalogenose reacts with an hydroxy compound in the presence of a condensing agent such as silver oxide. The procedure is carried out in an inert solvent, chloroform or benzene—




Various condensing agents have been used, the configuration of the final product being effected by the choice. Silver oxide or silver carbonate leads to the formation of beta isomers whereas mercuric acetate yields either alpha or beta forms, depending upon its concentration. The acetobrom sugars have proved to be the most suitable of the acetohalogenoses for this condensation.

Helferich and his co-workers prepared β-*d*-glucose-1,2,3,4-tetraacetate and β-*d*-mannose-1,2,3,4-tetraacetate. This made possible the synthesis of oligosaccharide acetates in which the first carbon atom of one saccharide unit and the sixth carbon atom of the second unit are joined through a biosidic linkage. The free sugar may then be obtained by deacetylation of the acetate. The reaction resulting in oligosaccharide acetates may be represented as follows—




Helferich prepared a number of new oligosaccharide acetates by condensing acetohalogenoses—such as acetobromoglucose, acetobromogentiobiose, and the acetobromo derivative of gentiobiosidoglucose—with β-*d*-glucose-1,2,3,4-tetraacetate. Most of these were obtained in yields of 20-25% of the theoretical.

Recently, Reynolds and Evans secured considerably higher yields by modifying the experimental procedure and by using anhydrous calcium sulfate as an internal desiccant. In this manner, they also obtained β-gentiobiose octaacetate in yields of 75–80%, and extended this synthesis into the mannose series.

# Eastman Organic Chemicals as Analytical Reagents

## REAGENTS FOR COBALT

### Pyridine

Ostroumov: *Zavodskaya Lab.*, 7, 20 (1938)

Cobalt salts form crystalline sulfides when precipitated by hydrogen sulfide, in the presence of pyridine. A neutral or slightly acid solution of the salt is treated with a solution of pyridine chloride (for cobalt chloride) or pyridine nitrate (for cobalt nitrate). After diluting with water and heating, the mixture is treated with an excess of pyridine; then a current of hydrogen sulfide is bubbled through it for 30 minutes. The precipitated cobalt may be determined as $CoSO_4$, in the usual manner. Nickel salts react similarly, but are readily soluble in nitric acid.

### Dimethylglyoxime

Nilssen and Paulsen: *Tids. Kjemi Bergvesen*, **20**, 52 (1940)

A solution of cobalt in the trivalent state is treated with ammonium hydroxide and dimethylglyoxime, and filtered if necessary; a few drops of hydrogen peroxide are added and the mixture heated to boiling. Two drops of sodium polysulfide solution, prepared by boiling sodium sulfide with 3–5 mols of sulfur, are then added. A clear blue color indicates the presence of cobalt; but, if the concentration is very small, the color of the polysulfide may cause a greenish shade. None of the common ions interfere and the sensitivity of the test is approximately 1:5,000,000.

### Ethylenediamine

Weingarten: *Marshall Coll. Rev.*, 2, 27–29 (1938)

Ethylenediamine can be used to effect a quantitative separation of cobalt and nickel when they are present, in solution, in concentrations of 0.1N to 0.01N. Sufficient ethylenediamine is added to make the solution of the two metals decidedly alkaline, and then 5 cc. in excess. Next, 10 cc. of hydrogen peroxide are added to the mixture; after frothing has ceased, 3 gm. of ammonium sulfate are added and the solution allowed to stand for several minutes. If it is red instead of pink after the hydrogen peroxide treatment, the operation is repeated. The nickel complex separates as violet crystals which are filtered off and redissolved; then the entire procedure is repeated, to remove occluded cobalt.

### α-Nitroso-β-naphthol

Takagi and Nagase: *J. Pharm. Soc. Japan*, **56**, 574-577 (1936)

To a solution of 0.005–0.05 gm. of cobalt in 100–150 cc. of water is added 0.2 gm. of α-nitroso-β-naphthol; after acidification with acetic acid, and boiling, the cobalt is precipitated. The compound formed is $(C_{10}H_6O_2N)_3CoH_2O$, and decomposes at 306.5–307.5°; upon ignition $Co_3O_4$ is obtained.

### Ammonium Thiocyanate

Savari: *Rev. col. farm. nac. Rosario*, **6**, 159 (1939). Idem: *Anales farm. bioquim (Buenos Aires)*, **11**, 4 (1940)

One drop of a mixture of equal volumes of 0.05M resorcinol and 0.05M sodium nitrite is added to 1 cc. of a solution containing less than 0.1 gm. of cobalt per liter. One drop of 5N hydrochloric acid is then added and the solution thoroughly mixed. Finally, 5 cc. of 20% ammonium thiocyanate are introduced and the solution shaken for two minutes, with 5 cc. of ether, in a separatory funnel. The red ether layer is removed and compared with standards, in a colorimeter. Copper can be present in the solution in concentrations up to 10 times as great as that of the cobalt, without causing interference.